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ORIGINAL ARTICLE

A phase III, randomized, controlled, superiority trial evaluating the fibrin pad versus standard of care in controlling parenchymal bleeding during elective hepatic surgery

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Abstract

Introduction: Haemostasis after liver resection may be difficult to achieve as a result of the presence of challenging bleeding, the anatomic landscape of the liver and the quality of tissue making up the hepatic parenchyma. The fibrin pad (FP) is a topical absorbable haemostat designed to be effective in a variety of tissues and across multiple bleeding intensities. This is the first clinical trial to evaluate the hemostat's safety and effectiveness in controlling bleeding during elective hepatic resection.

Methods: This prospective, randomized, controlled superiority trial enrolled 104 subjects undergoing elective hepatectomy in 5 countries. After parenchymal transection, subjects with an appropriately defined target bleeding site (TBS) were stratified according to the type of hepatic parenchyma and immediately randomized 1:1: FP versus Standard of Care (SoC). SoC comprised manual compression with the use of an approved topical absorbable haemostat. The primary endpoint was haemostasis at 4 min from identification of the TBS, with no re-bleeding requiring re-treatment prior to abdominal closure. Results were stratified for both normal and abnormal (steatosis or cirrhosis) hepatic parenchyma. All subjects were followed for 60 days post-operatively.

Results: The intent-to-treat (ITT) analysis showed an overall treatment difference of 53.0% ($P < 0.001$), 82.5% (33/40 FP) versus 29.5% (13/44 SoC) in achieving haemostasis at 4 min with no re-bleeding requiring treatment up to wound closure. The per protocol analysis showed an overall treatment difference of 65.7% ($P < 0.001$), with 33/35 successes (94.3%) in the FP group and 12/42 in the SoC group (28.6%). The stratification results showed treatment differences between the normal parenchyma group, 63.6% (95.8% FP versus 32.3% SoC $P < 0.001$) and a larger difference of 72.7% in the abnormal parenchyma group (90.9% FP versus 18.2% SoC $P = 0.0003$). Post-operative intra-abdominal fluid collections were less frequent in the FP group (3.4% FP versus 13.3% SoC $P = 0.059$). There was no difference in the safety profile between the FP or SoC groups.

Conclusions: The FP is safe and effective when used as an adjunct to achieve haemostasis during hepatic surgery. The success rate of achieving haemostasis with a FP remained high compared with the SOC group, especially in steatotic or cirrhotic liver tissue where the control success rates diminish. In addition, FP treatment of hepatic parenchymal surfaces may reduce the risk of post-operative biliary and fluid collections.

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Introduction

Bleeding during surgery can be focal, regional or generalized. Focal bleeding usually comes from an open vessel and can be addressed with either suture ligation or, if minor, thermal means

such as diathermy. Generalized bleeding usually reflects a systemic issue with coagulation and requires the administration of blood and blood products as well as specific coagulation factors. Regional bleeding is often more difficult to control as it arises from a specific area, often a tumour bed or parenchymal surface. Focal techniques can be used as well as widespread application of thermal energy with diathermy or argon beam coagulation or the application of surgical packs.

The liver can represent a particular challenge in terms of regional bleeding. Once the hepatic parenchyma has been divided during a liver resection a bare parenchymal surface is left. Bleeding can arise from this and may be exacerbated by high venous pressures, intermittent in flow occlusion causing periods of relative ischaemia[1–3] and fragile parenchyma which may tolerate suture application poorly. Analysis of the causes of blood loss during a hepatectomy shows that significant bleeding can occur from the parenchymal surfaces during the split rather than from control of the major inflow or outflow structures.[1] Furthermore, blood loss can be significantly greater in patients with abnormal parenchyma as a result of cirrhosis or steatosis a undergoing hepatectomy emphasizing the advantage of a normal parenchyma in managing a haemorrhage by conventional means.[4] In addition, there is increasing evidence that transfusion of blood or blood-derived products can be associated with significant morbidity. Consequently, there is increased focus on reducing blood loss and eliminating transfusion requirements in all forms of hepatic surgery.[3]

The fibrin pad (FP) is a novel means of treating regional bleeding during surgical procedures. The FP is made up of a flexible matrix of polyglactin 910 filaments needle punched into one side of a backing of oxidized regenerative cellulose 10.2 cm square. Human thrombin and human fibrinogen are then bound to the polyglactin filaments (Fig. 1). The FP has a biological side with an enhanced surface area as a result of the presence of multiple polyglactin filaments with bound thrombin and fibrinogen. The other side is non-biological and consists only of oxidized regenerative cellulose. The FP works by applying the biological side to an area of active bleeding. Activation of thrombin and fibrinogen results in the development of a local clot and adherence of the FP to the surface. The FP is absorbable and remains *in situ* at the end of the surgical procedure. The FP has been assessed in two previous randomized trials of moderate (Clinicaltrials.gov identifier: NCT00658723) and severe soft tissue bleeding (Clinicaltrials.gov identifier: 00977925) and has been shown to be safe and effective in these clinical settings.[5,6]

This investigation was designed to assess the effectiveness of the FP at controlling parenchymal edge bleeding after an elective hepatectomy. This trial was also designed to define the ability of the FP to achieve haemostasis in both normal and cirrhotic or steatotic livers after hepatectomy, to assess the safety of the FP in this setting.

Materials and methods

This was a randomized, controlled superiority study evaluating the effectiveness of the FP compared with standard of care (SoC) methods utilized to control bleeding in hepatic parenchyma after an elective liver resection (Clinialtrials.gov identifier: NCT01166243). The trial was carried out in 10 centres in Europe, United Kingdom, Australia and New Zealand (see Acknowledgements) supervised by an investigator in each centre. The trial was designed to align with the CONSORT guidelines and to be reported in a manner consistent with the CONSORT statement.[7]

Patients

Patients undergoing a partial hepatectomy were recruited for the trial by the investigators and local trial coordinators. Patients were

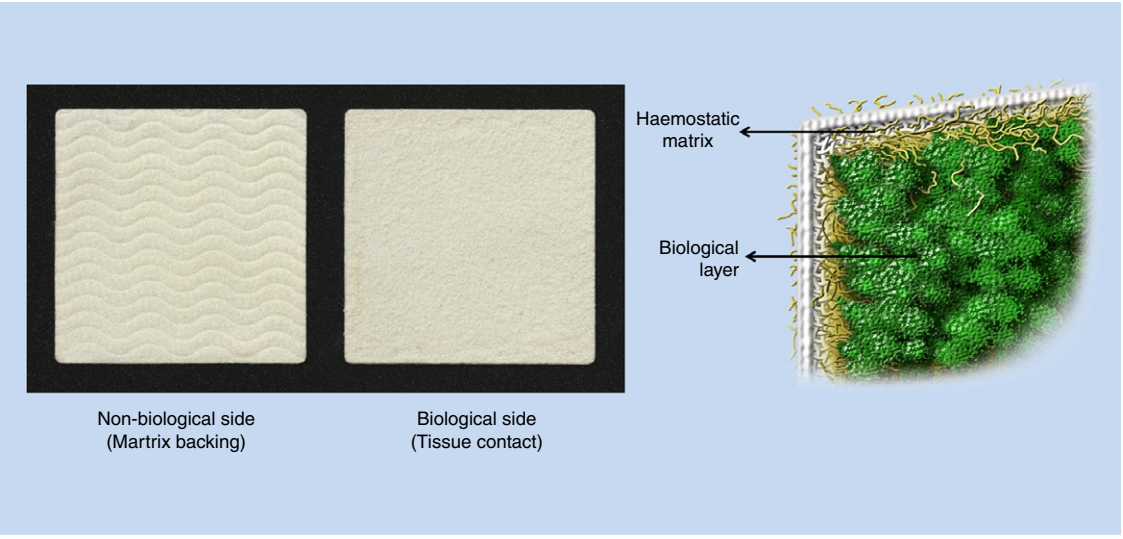

Figure 1 The fibrin pad non-biological side (left), biological side (middle) and graphic demonstrating trilayer composition (right)

Table 1 Schedule of study events

Procedure	Screening	Baseline	Surgical procedure	Post-surgery to discharge	Day 1 and 3,4 or 5	30-day follow-up	60-day[d]
Inclusion/exclusion	X	X	X				
Informed consent	X						
Demographics	X						
Medical history	X						
Concomitant medications	X	X	X	X		X	X
Physical exam	X			X		X	
Complete blood count[a]	X			X		X	
Liver function tests[b]	X		X	X		X	
Coagulation studies[c]	X			X		X	
Haemoglobin, Hct only	X		X	X	X		
Pregnancy test (if applicable)	X						
Viral safety	X						
Randomization			X				
Treatment application			X				
Intra-operative details			X				
Determination of haemostasis			X				
Bleeding & thrombotic complications			X	X		X	X
Adverse events			X	X		X	X
Operative/surgical information			X	X			

[a]All complete blood counts included are differential.
[b]Liver function tests included serum bilirubin, aspartate transaminase (AST), gamma glutamyl transferase (γGT), total protein and albumin concentrations.
[c]Coagulation studies included prothrombin time (PT), partial thromboplastin time (PPT), international normalized ratio (INR), platelet count and fibrinogen determinations.
[d]60-day follow-up could be conducted via a telephone interview.

considered eligible for enrolment if they were older than 18 years of age and required urgent or elective hepatic resection and were able to provide written, informed consent. Patients were excluded from enrolment if admitted for trauma surgery, undergoing a liver transplant for fulminant hepatic failure, had active sepsis around the liver, a known tolerance to blood products or one of the components of the FP, were unwilling to receive blood products, were a known and current alcohol or drug abuser, were pregnant or breast feeding, or had participated in another investigational drug or device research study within the previous 30 days.

Potentially eligible patients were reviewed in outpatient clinics and the trial discussed. Patients were enrolled after the consent process and then were screened (Table 1). This involved a full history, physical examination, determination of a full blood count, liver function tests, coagulation studies and, if appropriate, a pregnancy test. A total of 5 ml of blood was also stored at −80°C, with the patient's specific consent, for up to 5 years for later determination of viral titres if required. Screening occurred within 21 days of the surgical procedure. The patient's thromboembolism risk was also assessed using the system of Caprini.[8] Further review of potential exclusion criteria and medications was undertaken on admission for a hepatectomy (baseline, Table 1).

Study procedure

Potentially eligible patients were admitted under the operating surgeon. The surgical procedure including hepatic mobilization, vascular control, parenchymal division and use of post-operative surgical drains was performed according to the surgeon's standard practice. Both the FP and any other absorbable haemostatic products that constituted routine standard of care (such as oxidized regenerative cellulose) were prepared[9] and available in the sterile field on the instrument trolley. Patient randomization occurred after the resection if the surgeon encountered an appropriate target bleeding site in the hepatic parenchyma. The target bleeding site (TBS) was defined as a bleeding site that, after 30 s of firm manual compression, had persistent bleeding that required immediate attention and where conventional methods of control (suture, ligation or cautery) were felt to be ineffective, impractical or inappropriate. At this point randomization occurred by opening the appropriate randomization envelope and a stopwatch started simultaneously.

Subjects randomized to SoC received continuous manual pressure with a gauze and oxidized regenerative cellulose for a total of 4 min after randomization. Subjects randomized to FP were treated with a FP over the TBS and continuous firm manual

compression which was released 4 min after randomization. The total period of manual compression was somewhat less than 4 min taking into account the time required for randomization and the transfer of the SoC or FP from the theatre instrument table to the surgeon and its application. Haemostasis was assessed at 4 min from randomization, at 10 min from randomization and at the completion of surgery immediately prior to fascial closure.

Prior to randomization, the site and nature of the primary operative procedure was recorded as well as the type of hepatic parenchyma (normal, cirrhotic or steatotic). The area of the TBS and whether it was arterial, venous or mixed and pulsatile or non-pulsatile was noted after randomization. The area of the transected hepatic parenchyma was measured directly with a small, sterile hand ruler.

Application of the fibrin pad and standardized surgeon training

The FP has a biological side in which the surface area has been increased by the application of multiple polyglactin filaments. Human thrombin and fibrinogen are bound to these filaments. The pad functions by careful application of the biological side to the bleeding surface. The FP can be only handled by the non-biological side and any moisture applied to the FP will result in early activation of thrombin and fibrinogen and a loss of its efficacy. In addition, the FP must be closely applied to the surface so that it conforms to the tissue. The FP must be closely approximated to tissues and wrinkles should be avoided during application to maximize effectiveness. Consequently, while the FP is straightforward to use, some training and understanding of its composition and mechanism of action are necessary.

Prior to the trial commencement, all surgeons and trial coordinators involved in this investigation attended full-day teaching sessions on the use of the FP and an opportunity was given to use the FP under careful supervision on a number of biological models of bleeding in various sites. In this way the application technique of investigators was standardized as well as clearly defining the size and severity of the TBS required for patient randomization. Teaching videos of example TBS and correct application of the FP were also available. In addition, the study included a 'run in' phase in which the first two eligible subjects for each participating investigator surgeon without prior experience of the FP was not randomized and had their target bleeding sites treated with the FP.

Definition of target bleeding site

The TBS was defined as a bleeding site that, after 30 s of firm manual compression, had persistent bleeding that required immediate attention and where conventional methods of control (suture, ligation or cautery) were felt to be ineffective, impractical or inappropriate. The TBS was also required to be a size that could be adequately covered by a single 10.2 cm by 10.2 cm FP. Bleeding from large arteries or veins where, the injured vascular wall required repair with the maintenance of vessel patency, was excluded. The FP was not used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding. In this investigation, the aim was to use the FP in the clinical setting where bleeding occurs from the parenchymal surface after a partial hepatectomy. In this setting, heat-based methods of coagulation are often inadequate and the surface is fragile and may not tolerate the application of sutures.

Definition of post-operative bile leak

A bile leak was defined as the presence of bile containing fluid in a drain. The bilirubin concentration in the fluid was required to be at least three times higher than the upper normal serum levels in patients with a normal post-operative serum bilirubin or a 50% higher bilirubin level in fluid than serum in patients with post-operatively elevated serum bilirubin levels.

Management of protocol violations

All protocol deviations were recorded and classified as major (one that may have an impact on the randomization assignment or an impact on the primary endpoint) or minor. All protocol deviations were reviewed by medically qualified monitoring personnel and the study team prior to database lock. All subjects were analysed on an intention-to-treat (ITT) basis.

Safety and monitoring

The protocol, consent and patient information documents were submitted by each investigator to the appropriate independent Ethics Committee or Institutional Review Board. Approval from these organizations was obtained and documented prior to any study-related procedure being undertaken. The study was conducted in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (1996),[10] the US Food and Drug Administration (FDA) regulations (Title 21 Code of Federal Regulations [CFR] Parts 50, 54, 56 and 312),[11] the Declaration of Helsinki (2008),[12] the European Union Trial Directive (2011/20/EC, May 2001) and the EU GCP Directive (2005/28/EC).[13]

An independent Data Safety Monitoring Board (DSMB) was established and reviewed all data for any potential safety issues for the duration of the study. A Clinical Events Committee (CEC) was also created to adjudicate adverse events that were potentially related to the TBS bleeding or thrombotic events. Membership of these boards was independent with no affiliation to the trial sponsor.

All adverse events were recorded and reviewed by the DSMB. Serious adverse events were defined as adverse events that potentially prolonged the duration of hospital stay.

Statistical methods

The trial reporting and analysis were aligned with the CONSORT check list. The sample size was determined based on previous clinical trials utilizing the FP in severe soft tissue bleeding and assumed that the FP performance would be no worse than 75%

with at least a 25% treatment difference with standard of care.[14] Random allocation of patients to the FP or SoC groups was generated by a computer program and validated by a secondary statistician. The allocation was on sequentially numbered concealed envelopes.

Three analysis sets were defined. ITT set consisted of all randomized subjects. Subjects who did not complete the procedure after randomization were considered failures and included in the ITT analysis. An evaluable set (or per protocol; PP) consisted of all ITT subjects who had no major protocol deviations, and a safety set consisted of all subjects who received treatment (the ITT set plus the 'run in' phase patients). Patients were randomized to FP or to SoC with a 1:1 allocation ratio. The sample size required was not fixed but was dependent on the data with the first planned interim data analysis at 80 patients in the ITT group. This was the only analysis performed and the trial was stopped at this point.

The Whitehead triangular test[15] for a binary response variable was utilized (PEST 4.4 software; Department of Mathematics and Statistics, University of Lancaster, Lancaster, UK) for primary response variables with a two-sided alpha of 0.05 and power 0.9. The assumed success rate in the control arm was 50% and in the FP arm was 75%. Direct comparison of secondary effectiveness variables between the treatment and control group was undertaken using Wilcoxon's Rank-Sum test and 95% confidence limits were calculated using a distribution-free approach (SAS, Version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Patients

One hundred and four patients were included in the trial. Twenty non-randomized subjects were treated with the FP during the run-in phase of the study. The safety set consisted of all randomized patients as well as the 20 patients treated with FP during the 'run in' phase and comprised 59 patients treated with FP and 45 patients treated with SoC. This 'run in' phase was incorporated to allow surgeons familiarity with the FP under operative conditions. The ITT set, defined as all randomized patients only, consisted of 40 patients treated with FP and 44 patients treated with SoC (Fig. 2). One subject was randomized to FP but received SoC and this subject was analysed in the FP group for the ITT set and the SoC group for the safety set. Analysis of efficacy data was performed on both the ITT and safety set whereas safety variable analysis was carried out on the safety set. Patient demographics for the ITT set are summarized in Table 2, whereas patient diagnoses, operative procedures and parenchymal characteristics are summarized in Table 3.

Surgical drains were placed at the end of the procedure in 44/59 (74.6%, median 1 drain, range 1–3 drains) of patients treated with the FP and 36/45 (80%, median 1 drain, range 1–6 drains) of patients treated with SoC.

Classification of TBS

The characteristics of the TBS are summarized in Table 4.

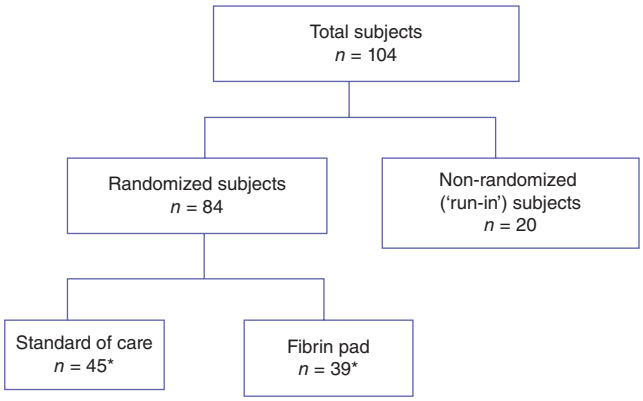

Figure 2 Disposition of study subjects by treatment (safety set). *One subject was randomized to the fibrin pad (FP) but received standard of care (SoC) and this subject is analysed in the FP group for the intention-to-treat (ITT) set and the SoC group for the safety set

Table 2 Demographic details of patients in the intention-to-treat (ITT) set

Category	Fibrin pad (*n* = 40)	Standard of care (*n* = 44)
Median age (range)	65 (31–82)	65.5 (39–82)
18–49 years	6	7
50–64 years	12	14
65–74 years	13	13
≥75 years	9	10
Gender		
Male	24	24
Female	16	20
Median body mass index kg/m^2 (range)	27 (15–41)	25 (18–43)
Underweight	1	1
Normal	13	15
Overweight	12	17
Obese	13	9
Morbidly obese	1	1
Smoking history		
Yes	24	22
No	16	22
Venous thrombosis risk score[8]	14.7 ± 2.6	14.3 ± 2.4

Treatment efficacy

The primary efficacy endpoint was the proportion of patients achieving haemostasis (defined as no detectable bleeding) at the TBS 4 min after randomization with no re-bleeding requiring treatment at the TBS at any time prior to wound closure. At 4 min after randomization with the release of manual compression, 34/40 patients (85%) in the FP achieved haemostasis compared

Table 3 Diagnoses, operative procedures and parenchymal type for the safety set

Category	Fibrin pad (*n* = 59)	Standard of care (*n* = 45)
Diagnosis		
Metastatic colorectal cancer	44	34
Hepatocellular carcinoma	8	7
Cholangiocarcinoma	1	3
Haemangioma	2	1
Other	4	0
Duration of surgery (mean: range)	191 min (60–584)	184.4 min (75–397)
Operative procedures		
Anatomic	38	31
Right hepatectomy	18	15
Left hepatectomy	6	5
Left lateral sectionectomy	5	4
Segmentectomy	3	3
Extended right hepatectomy	4	1
Extended left hepatectomy	0	1
Posterior right sectionectomy	1	2
Subsegmental resection	1	1
Non-anatomic	17	9
Other	4	5
Hepatic parenchyma		
Normal	41	33
Abnormal	18	12
Cirrhotic	3	5
Steatotic	13	3
Other	2	4

Table 4 Summary of the characteristics of the target bleeding site (TBS) for the fibrin pad (FP) and standard of care (SoC)

	Statistic	ITT Set		Safety set	
		FP (*n* = 40)	SoC (*n* = 44)	FP (*n* = 59)	SoC (*n* = 45)
Total transected area (cm^2)	Median (range)	64 (3–225)	50 (10–200)	70 (3–316)	50 (10–200)
Area of TBS (cm^2)	Median (range)	4.0 (0.3–81.0)	4.0 (0.1–49.0)	7.1 (0.2–81.0)	4.0 (0.1–49.0)
Source of bleeding					
Arterial	Number	2	2	3	2
Venous	Number	20	24	36	24
Mixed	Number	18	18	20	19

ITT, intention to treat.

with 17/44 (38.6%) in the SoC group. The number of subjects with haemostasis at 4 min and requiring no treatment for rebleeding was 33/40 (82.5%) in the FP group and 13/44 (29.5%) in the SoC group ($P < 0.0001$) if missing data are imputed as failures in both treatment groups (Table 5). The efficacy of the FP was comparable in both normal and abnormal parenchymal groups although SoC was less effective in patients with abnormal parenchyma (Table 5). In the ITT set, seven patients treated with FP were considered treatment failures and all were included in the ITT analysis. In one patient bleeding was present at 4 min but not at 10-min compression. One patient was wrongly randomized to SoC because the wrong randomization envelope was opened. This patient was treated with SoC but included in the FP group for ITT analysis. One subject developed further bleeding from the TBS after the FP was dislodged at 9 min having achieved haemostasis at 4 min and this was the only patient treated with FP classified as rebleeding. One patient had an arterial bleeding point inappropriately treated with FP. This TBS was an exclusion criterion.

Table 5 Haemostatic success at 4 and 10 min from randomization [intention-to-treat (ITT) set]

Hepatic parenchyma	Fibrin pad	Standard of care	*P*-value	Treatment difference
Haemostasis at 4 min				
All	33/40	13/44	<0.001	53.0%
Normal	23/28	11/33	0.001	48.8%
Abnormal	10/12	2/11	0.001	65.2%
Haemostasis at 10 min				
All	38/40	30/44	0.018	25.2%
Normal	27/28	23/33	NS	24.5%
Abnormal	11/12	7/11	NS	28.1%

NS, non-significant.

Finally, two subjects had the FP placed and haemostasis was achieved but not assessed until 4 min 30 s and 4 min 31 s after randomization. Both were considered treatment failures for primary efficacy.

In the ITT analysis, the absolute time to haemostasis was 4 min (range 4 to 13.2 min) compared with 9.7 min (range 4 to 31.3 min) in the SoC group ($P < 0.001$). Similar results were obtained in the safety group analysis [4 min (range 4 to 13.2 min) versus 9.7 min (range 4 to 31.3 min) $P < 0.001$].

Blood loss and transfusion requirements

The volume of blood lost during surgery was estimated by the investigator taking into account measured losses in suction and surgical swabs. The median estimated blood loss was 300 ml (range 20–2800 ml) in the FP group and 400 ml (range 50–3000 ml) in the SoC group ($P = 0.491$). Similar figures were estimated in the safety set. In the ITT analysis, 12/40 (30%) patients in the FP group and 18/44 (40.9%) in the SoC group required a red cell transfusion in the period between the commencement of surgery and the day-30 assessment ($P = 0.42$).

Post-operative course

There was no difference in the post-operative intensive care unit stay for patients treated with the FP or SoC (67.7 h ± 52.3 h versus 36.5 h± 25.4 h) or in total hospital stay (9.4 ± 4.4 nights in FP group versus 10.9 ± 6.3 nights in the SoC group). No patient died within 60 days of surgery and there were no deaths in either treatment group during the study.

Post-operative drains and bile leak

Bile leaks occurred in 5/59 (8.5%) of patients treated with FP and 5/45 patients treated with SoC (11.1%) in the safety set ($P < 0.059$). A radiologically guided percutaneously placed drain was used to treat one of five patients in the FP group and two of five patients in the SoC group. No action was required in the other patients. Post-operative fluid collections at the liver bed were present in 2/59 (3.4%) of the FP group and 6/45 (13.3%) in the SoC group ($P < 0.059$).

Table 6 Adverse events occurring in ≥ 10% of patients treated with either the fibrin pad (FP) or standard of care (SoC)

System	Adverse event	Number (%) patients experiencing an event	
		FP ($n = 59$)	SoC ($n = 45$)
General	Peripheral oedema	4	9
	Pain	15	18
	Pyrexia	15	12
Haemopoietic	Anaemia	14	11
Cardiac	Tachycardia	6	5
Gastrointestinal	Constipation	22	20
	Intra-abdominal collection	2	6
	Nausea	31	28
	Vomiting	20	14
Metabolic	Hyperglycaemia	1	5
	Hypokalaemia	14	11
	Hypomagnesemia	9	3
Musculoskeletal	Arthralgia	8	7
Nervous	Dizziness	9	7
	Anxiety	8	3
	Confusional state	3	5
	Hallucination	3	5
	Insomnia	9	7
Renal	Incontinence	0	5
Respiratory	Pleural effusion	7	8
Vascular	Hypertension	6	10
	Hypotension	21	17

Adverse events and safety

A total of 462 adverse events occurred in patients treated with the FP, with 56/59 (94.9%) experiencing at least one event of which 23 of the events were categorized as serious. In comparison there were 449 adverse events documented in 43 of 45 patients treated with SoC, and thirteen were classified as serious. The adverse events occurring in both treatment groups are summarized in Table 6.

Adverse events that were considered to be possibly or probably related to study treatment occurred in 3/59 (5.1%) in the FP group and no patients in the SoC group. The three adverse events with a possible relationship to treatment with the FP were an intra-abdominal collection after a hepatectomy. This was diagnosed with an abdominal CT scan on post-operative day 5 and treated with insertion of a drain. In a second patient, a total of 1480 ml of serosanguinous fluid was drained into a surgical drain within 24 h of liver resection. This was treated with a transfusion and resolved without operative intervention. Finally, a third patient lost 2000 ml of blood into a surgical drain in the first 48 h after a hepatectomy. This was managed with transfusion and correction of underlying coagulation anomalies and settled within 48 h without requiring re-operation. In these latter two patients there was no reoperation or further imaging studies to confirm TBS rebleeding. Within the SoC group, no causal relationship to any adverse event could be established as this was a standard surgical technique to achieve haemostasis rather than an investigational product.

All adverse events were assessed for any potential relationship to rebleeding at the TBS. One case of an intra-operative haemorrhage and one case of a post-operative haemorrhage were assessed as being potentially related to rebleeding at the TBS.

In the safety set, 2/45 (4%) patients treated with SoC developed thrombotic complications (vena caval thrombosis after a caval resection and portal vein thrombosis) and 1/59 (2%) patients treated with the FP developed a proven pulmonary embolism. No other thromboembolic events were documented.

Discussion

This was a randomized, controlled superiority study to evaluate the effectiveness of the FP compared with SoC utilized to control bleeding in hepatic parenchyma, after a hepatectomy, for which standard methods of achieving haemostasis were ineffective, impractical or inappropriate. The trial was randomized to avoid treatment bias and to ensure that the patient groups were comparable. Stratification for the type of hepatic parenchyma was undertaken to ensure a balanced distribution of patients with normal and abnormal parenchyma across the treatment groups and to enable some conclusions to be drawn regarding the efficacy of the FP in a variety of conditions. Formal training of participating surgeons was also required to ensure that the FP was correctly applied, the definition of TBS uniformly applied and the conduct of the trial was standardized – particularly the timing between randomization, pad application and assessment of haemostasis at 4 and 10 min. In addition, a 'run in' phase was also included so that the first two patients randomized in the operating room were treated with the FP to further embed the procedures necessary for the correct conduct of the trial. The control arm of the trial was manual compression with either a gauze swab plus or minus oxidized regenerative cellulose. This was chosen as these are widely available products, have been used as comparison in previous trials of the FP and constituted a reasonable and acceptable international standard of care. Finally, careful consideration was given during the trial design to a blinded design with a placebo pad as the control group. This would have required manufacture of a placebo pad with the same controls as the FP which was not feasible and, as the FP is made up of three separate products, would have lead to a trial with at least two experimental arms.

The accurate definition of the TBS was crucial in standardizing the trial conditions across the various centres and was carefully developed to enable other trials of regional haemostatic products to be undertaken in the future using a reproducible format. The TBS was defined as the first actively bleeding site identified in the hepatic parenchyma after transection. The TBS also had to be non-responsive to 30 s of manual compression and require the surgeon's immediate attention. These two criteria were set to define a significant bleeding point, rather than minor surface ooze, that if left untreated would have significant haemodynamic consequences for the patient. The time of 30 s manual compression was deliberately chosen to reflect the common practice of surgeons to treat minor bleeding with short periods of compression and to eliminate the randomization of patients with clinically insignificant bleeding. In addition, conventional methods of control (suture, ligature, cautery and argon beam coagulation) were deemed to be ineffective, impractical or inappropriate. This final criterion effectively excluded minor blood loss that could be addressed with cautery or argon beam and discrete open vessels that should be appropriately dealt with by suture or ligature. Finally the TBS had to be a site where occlusion of the injured surface vessels was required to achieve haemostasis. This specifically excluded large defects in arteries or veins where the wall required repair with maintenance of vessel patency. Persistent exposure of the FP to blood flow and pressure during healing and absorption is contraindicated because of the possibility of later arterial pseudoaneurysm and the theoretical possibility of widespread intravascular activation of the coagulation cascade.

This investigation has demonstrated that the FP is superior to SoC in achieving parenchymal haemostasis after a hepatectomy. The FP achieved haemostasis in 82.5% of patients in comparison to SoC which was effective in achieving haemostasis in 29.5% of patients. This was a highly significant difference and resulted in the trial being stopped at the first interim analysis. In addition, the effectiveness of the FP was maintained in patients with abnormal hepatic parenchyma (90.9% patients versus 18.2% patients in the SoC group). This is an important finding as steatotic or cirrhotic parenchyma is technically more demanding to operate on and often blood loss is higher in these procedures. This is related to the increased fragility of the parenchyma, associated hepatic dysfunction and the technical difficulty of using sutures and other methods of coagulation on friable, fragile tissue. As hepatic resection is increasingly utilized to treat patients with primary and secondary hepatic malignancy, many patients are presenting for treatment with well-compensated cirrhosis or steatosis after preoperative chemotherapy[4,16] and the development of techniques to

undertake surgery in these patient groups is an area of focus for hepatobiliary surgeons. This trial has demonstrated that the FP will positively contribute to the management of these patients and provides further evidence that fibrin-based products have a significant role to play in the management of bleeding after a hepatectomy.[17] Finally, the high concentrations of fibrin and thrombin delivered to the site of bleeding by the FP indicate that it will remain effective in patients with depletion of endogenous clotting factors.

In this trial, while the patients treated with FP clearly achieved haemostasis before those treated with SoC, operative time, intensive care stay and overall hospital stay were similar. In addition, while the measured blood loss and transfusion requirements were lower in the FP-treated cases these did not reach statistical significance. However, the primary endpoint of this trial was the time taken to achieve inta-operative haemostasis and the statistical analysis and power calculations were undertaken with this aim. Transfusion requirement and hospital stays were secondary endpoints. The strong trends shown in the data suggest that an adequately powered study, with these as primary endpoints, utilizing the FP would achieve a positive result.

The effectiveness of the FP in achieving haemostasis is related to its mode of action. Activation of the fibrinogen and thrombin on the biological surface results in local clot formation. Significantly the surface does not need to be dry but the pad must be applied closely to the surface, even if it is irregular. This results in adherence of the FP to the tissue forming a tight and adhesive seal. Failure of the FP can occur if it is moved before the adherence occurs or if the FP does not conform to the tissue. This is a particular risk in the liver if the FP is incorrectly applied to focal parenchymal defects so that they are bridged rather than covered. This can result in ongoing bleeding in the defect and eventual lifting of the FP. In this study, there were seven treatment failures in patients treated with the FP. Two patients achieved haemostasis but this was not assessed at 4 min and they were counted as treatment failures and one patient was wrongly randomized to SoC but was counted as a FP failure. In one patient with a cylindrical defect after a metastatectomy the FP did not conform exactly to the tissue defect so had to be replaced, and in one patient an arterial bleed which should have been treated with suture ligation bled through the FP. Of the remaining two patients, hemostasis was achieved at 4 min but the pad was manually dislodged at 9 min with hemostasis re-established using another FP and in the final patient seepage at the edge of the FP continued at 4 min but was absent at 10 min following further manual compression. While these patients were correctly analysed as treatment failures it is important to note that there was no instance of the FP not functioning, when correctly applied.

A further observation in the trial was the effect the FP had on the frequency of post-operative bile leaks and collections at the surgical site. Overall, the presence of post-operative intra-abdominal collections was less frequent in the FP-treated patients (3.4% versus 13.3% in the SoC patients) and the incidence of post-operative bile leaks was 5/59 (8.5%) in the FP group versus 5/45 (11.1%) in the SoC group. For both intra-abdominal collections and bile leaks the level of significance was marginally greater than 0.05. Other investigators have demonstrated the importance of adherence strength of fibrin-based products at maintaining clot integrity at the liver edge[18] and also the potential role this effect has in sealing the liver edge and reducing the risk of post-resection bile leak and intra-abdominal collection.[19]

One of the potential attractions of the FP is its safety profile. It is a composite of oxidized, regenerative cellulose and polyglactin fibres. Both of these materials have been in clinical use for several decades and are fully absorbed under physiological conditions. Human fibrinogen and thrombin are bound to the polyglactin fibres in high concentrations. The fibrinogen and thrombin was obtained from pooled plasma and is treated for known infective agents. This treatment involves screening for all known viral markers followed by solvent detergent treatment for inactivation of lipid enveloped virus. The plasma is then pasteurized and nanofiltered for non-specific virus inactivation and removal. As part of this trial, patients treated with FP had blood banked, with their consent, for 5 years after randomization to enable any retrospective testing for viral or other infections should this become necessary in the future.

In the development of this trial, infected collections at the operative site and thromboembolic disease were recognized as potential complications of FP application. However, only three patients treated with FP were considered to have had an adverse event potentially related to the FP. One of these was an intra-abdominal collection managed with drainage, and two patients had post-operative drain losses managed conservatively. Only two patients in the SoC group and one patient in the FP group developed thromboembolic complications. All patients had a high-risk score pre-operation for thromboembolic disease indicating that the patient population overall was a high risk one. However, this study and two other trials utilizing the FP in moderate and severe soft tissue bleeding have not confirmed any increased risk of thromboembolic events in patients treated with the FP.

This investigation has confirmed that the FP is safe and effective at treating parenchymal bleeding after an elective hepatectomy in a variety of parenchymal types. It has also been shown to be effective in managing soft tissue bleeding in a variety of soft tissue sites particularly tumour beds after resection, the pelvis after resection of the rectum and the urinary bladder, the renal bed after nephrectomy and in the mediastinum and thoracic cavity. The FP is straightforward to store and use and does not require complex preparation. It has not yet been assessed in the acute setting but the possibilities for its application in trauma surgery, damage control surgery and even as a field dressing are obvious. While the FP will never be a substitute for accurate and careful surgical technique it represents a significant advance in the field of regional haemostasis and it provides

surgeons with a significant addition to their intra-operative armamentarium.

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Conflicts of interest

None declared.

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